Remarks

Claims 22-25 were pending in the subject application. By this Amendment, claims 1-41 have been canceled; and new claims 42-62 have been added. The undersigned avers that no new matter is introduced by this amendment. Upon entry of this Amendment, claims 42-62 will be before the Examiner. Favorable consideration of the pending claims is respectfully requested.

The drawings of record are objected to for the reasons indicated by the draftsperson on form PTO-948. Submitted herewith are formal drawings meeting the requirements of 37 C.F.R. § 1.81-1.85 to replace the drawings of record in the subject application. Figure 13A has been separated into Figures 13A-1 and 13A-2, and Figure 13B has been separated into Figures 13B-1and 13B-2. The applicant has amended references to these figures in the specification accordingly. No new matter is introduced by these amendments.

Claims 22-25 are rejected under 35 U.S.C. §112, second paragraph, as indefinite. The Office Action indicates that claims 22-25 are indefinite with regard to the characterization of the claimed cells. The applicant respectfully submits that the claims are not indefinite; however, by this Amendment, the applicant has canceled claims 22-25, rendering this rejection moot. New claims 42-62 recite that each pluri-differentiated mesenchymal progenitor cell simultaneously expresses a plurality of genes that are markers for multiple cell lineages, wherein each of the markers is specific for a single cell lineage. Support for claims 42 and 50 can be found, for example, at page 11, lines 27-30, page 12, lines 4-7, and page 13, lines 23-31, of the specification as originally filed. Support for new claims 43, 44, 51, and 52 can be found, for example, at page 13, lines 28-31, page 15, lines 1-2, and page 16, lines 1-7, of the specification as originally filed. Support for new claims 45, 49, and 53 can be found, for example at page 27, lines 28-33, page 28, lines 4-33 (Table 1), page 29, lines 1-16, page 31, lines 15-33, and page 32, lines 11-28, of the specification as originally filed. Support for new claims 46 and 55 can be found, for example, at page 2, lines 6-12, page 13, lines 19-31, and page 26, lines 20-25, of the specification as originally filed. Support for new claims 47 and 55 can be found, for example, at page 32, lines 30-33, and page 33, lines 1-2, of the specification as originally filed. Support for claims 48, 49, 60, and 61 can be found, for example, at page 13, lines 28-31, page 15, lines 1-2, page 16, lines 1-7, page 27, lines 28-33, page 28, lines 4-33 (Table 1), page

29, lines 1-16, page 31, lines 15-33, and page 32, lines 11-28, of the specification as originally filed. Support for claims 57-59 can be found, for example, at page 5, lines 26-33, page 6, page 7, lines 1-20, and pages 17-22, of the specification, as well as the claims as originally filed. Support for claim 62 can be found, for example, at page 13, lines 28-31, page 15, lines 1-2, page 16, lines 1-7, page 27, lines 28-33, page 28, lines 4-33 (Table 1), page 29, lines 1-16, page 31, lines 15-33, and page 32, lines 11-28, of the specification as originally filed.

Claim 57 makes it clear that GvHD is synonymous with graft-versus-host disease. Support for this claim can be found, for example, at page 6, lines 22-26, of the specification as originally filed.

The applicant respectfully submits that the metes and bounds of the claimed invention are readily ascertainable by those of ordinary skill in the art. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claim 22 has been rejected under 35 U.S.C. §102(b) as being anticipated by Pittenger *et al.* (*Science*, 1999, 284:143-147) in light of Ager *et al.* (*Immune Receptor Supplement. Immunology Today*, 1997, pp. 1-35). In addition, claims 22-24 have been rejected under 35 U.S.C. §102(b) as being anticipated by Caplan *et al.* (U.S. Patent No. 6,010,696). The applicant respectfully submits that the cited references do not teach or suggest the claimed invention. However, as indicated above, the applicant has canceled claims 22-24, rendering this rejection moot. New claims 42-62 recite that each pluri-differentiated mesenchymal progenitor cell simultaneously expresses a plurality of genes that are markers for multiple cell lineages, wherein each of the markers is specific for a single cell lineage.

Pittenger *et al.* describe pluripotent mesenchymal stem cells isolated from the Friedenstein culture system, which are distinct from the cells of the claimed invention that are obtainable using the Dexter culture system. As indicated at page 12, lines 4-7, of the subject specification, the term "pluri-potential" refers to undifferentiated cells having the potential to differentiate into discrete mesenchymal tissues. In contrast, a "pluri-differentiated" cell of the subject invention is one that co-expresses genes specific for multiple lineages. As indicated at page 13, lines 25-31, of the subject specification, and as recited in the claims, these genes are expressed simultaneously. As indicated at page 144, second column, lines 16-28, of Pittenger *et al.*, the differentiation potential of the

pluripotent mesenchymal stem cells was evaluated by culturing the cells under lineage-specific culture conditions, *i.e.*, that were favorable to adipogenic, chondrogenic, or osteogenic differentiation. The pluripotent mesenchymal stem cells of Pittenger *et al.* were independently induced to differentiate along the three cell lineages, respectively, by: (i) treatment with 1-methyl-3-isobutylxanthine, dexamethasone, insule, and indomethacin; (ii) culturing centrifuged cell pellets without serum and with transforming growth factor-β3; and (iii) and exposure to dexamethasone, β-glycerol phosphate, and ascorbate, in the presence of FBS. Thus, the culture conditions required for differentiation along the three cell lineages were individualized and the cells did not simultaneously express markers for multiple cell lineages (see page 146 of Pittenger *et al.*). The Office Action indicates that the cells in Pittenger *et al.* were positive for various markers, such as "CD29, CD44, CD71, etc." and, therefore, pluri-differentiated in light of Ager *et al.* However, as indicated above, the cells of the claimed invention simultaneously express a plurality of genes that are markers for multiple cell lineages, wherein each of the markers is specific for a single cell lineage. In contrast, the "markers" listed at page 144, column 1 of Pittenger *et al.* are non-specific surface proteins, each of which are widely distributed within many cell lineages, as evidenced by Ager *et al.* For example, as indicated at pages 29-30 of Ager *et al.*, CD29 is expressed by fibroblasts, endothelial cells, NK cells, activated T cells, monocytes, neuronal cells, platelets, B and T cells, keratinocytes, epithelial cells, thymocytes, eosinophils, myelomonocytic cells, *etc.* As indicated at page 32 of Ager *et al.*, CD44 is expressed by haematopoetic cells, B and T cells, monocytes, neutrophils, epithelial cells, glial cells, fibroblasts, and myocytes. As indicated at page 12 of Ager *et al.*, CD71 is expressed by macrophages and proliferating cells. Thus, each of these surface proteins is ubiquitously expressed by a wide variety of cells types and, hence, not lineage-specific markers. Therefore, the cells described in the Pittenger *et al.* publication are not pluri-differentiated as recited in the currently pending claims.

The Caplan *et al.* patent describes mesenchymal progenitor cells propagated under and isolated from Friedenstein cultures. The Office Action indicates that the cells of the Caplan *et al.* patent are capable of differentiating into cells of various types of skeletal and connective tissues "depending upon environmental influences". However, as indicated above, each of the pluri-differentiated cells of the subject invention simultaneously expresses a plurality of genes that are

markers for multiple cell lineages, wherein each of the markers is specific for a single cell lineage. There is nothing within the Caplan *et al.* patent to indicate that the cells simultaneously express the diverse lineage-specific markers expressed by the pluri-differentiated cells of the subject invention. It is well settled in patent law that, in order to anticipate under 35 U.S.C. §102, a single reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claims. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991). The applicant respectfully submits that the cited references do not teach every element of the applicant's claimed invention and, therefore, do not anticipate the applicant's claimed invention. Accordingly, the applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b).

Claims 22-25 have been rejected under 35 U.S.C. §103(a) as being obvious over Caplan *et al.* and Pittenger *et al.* in light of Ager *et al.* and Bordignon *et al.* (*Haematologica*, 1999, 84:1110-1149). The applicant respectfully submits that the cited references, alone or in combination, do not teach or suggest the applicant's claimed invention.

As indicated above in response to the rejections under 35 U.S.C. §102(b), the Caplan *et al.* and Pittenger *et al.* references do not teach the pluri-differentiated cells of the subject invention as currently claimed. Neither reference describes a cell that simultaneously expresses a plurality of genes that are markers for multiple cell lineages, wherein each of the markers is specific for a single cell lineage. The Bordignon *et al.* publication suggests administration of mesenchymal stem cells propogated and isolated from the Friedenstein-type culture system for treatment of various disease states, such as modulation of graft-versus-host-disease (GvHD), but does not teach or suggest the pluri-differentiated cells of the claimed invention. Moreover, Bordignon *et al.* indicate the presence of hematopoietic stem cells and stem cells of non-hematopoietic tissues (also referred to as "mesenchymal stem cells") within the bone marrow that differentiate into cells roughly defined as mesenchymal, composed of a heterogeneous mixture of differentiated cells, instead of a single cell simultaneously expressing diverse lineage-specific markers. For example, at page 1136, column 1, Bordignon *et al.* state that

> stromal cells of the marrow microenvironment include fibroblasts, endothelial cells, reticular cells, adipocytes, osteoblasts and macrophages, the last, although of hematopoietic origin, being considered functional components of the regulatory

stroma.[316] The heterogeneous population of mesenchymal cells and their associated biosynthetic products have the unique capacity to regulate hematopoiesis. [317]

Therefore, the Bordignon *et al.* publication does not cure the deficiencies of the primary references (Caplan *et al.*, and Pittenger *et al.*). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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